Regulatory Requirements for Historical and New Smallpox Vaccines: Review of U.S. Regulations

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G7+ Workshop, Langen, Germany

September 5-6, 2002

Historical Smallpox Vaccine: Wyeth Dryvax â

- At present, only U.S. licensed smallpox vaccine
- Derived from New York City Board of Health (NYCBH) strain
- Prepared from calf lymph and stored as a freeze-dried product
- Vaccine supply limited
- No longer manufactured

Requirements for Historical Smallpox Vaccines

- Live vaccinia obtained from inoculated calves or chicken embryos
- Seed virus
  - Identify by historical records
  - Meets sterility requirements
  - Seed virus and every 3rd passage tested by rabbit scarification to show that original dermatotropic properties maintained

Requirements for Historical Smallpox Vaccines (cont.)

With regard to production

- Virus from calves
  - Quarantine, inoculation, incubation, harvesting, necropsy
- Virus from embryonated chicken eggs
  - Eggs from flocks free of specified agents, harvesting

Requirements for Historical Smallpox Vaccines (cont.)

With regard to testing

- Potency
- Safety
  - Testing for anaerobes, coliforms, hemolytic streptococci and coagulase-positive staphylococci, viable bacteria
- General safety
- Preservative
- Samples, protocols, official release

New “2nd Generation” Smallpox Vaccines Under Development (U.S.)

Cell substrate-derived

- Human diploid cells (MRC-5), continuous cell lines (VERO)
- Characterize/qualify master and working cell banks (e.g., adventitious agent testing, tumorigenicity)

Virus seed

- Derived from NYCBH vaccine strain
- Characterize/qualify master and working virus seeds (e.g., adventitious agent testing, comparability to licensed vaccines, including animal studies)

New Smallpox Vaccines: Production/Quality Control

Common Principles

- **Detailed manufacturing procedures: consistency of production**
- **Defined compatible components**
- **Product characterization: specifications**
- **Cell substrate characterization**
- **Adventitious agent testing**
- **Source of materials (e.g., BSE)**
- **Stability**

Standards of Licensure

- Safety
- Purity
- Potency
- Efficacy
- Manufacturing reproducibility
- cGMP Compliance

Clinical Evaluation of New Smallpox Vaccines

- Safety
- Efficacy
  - "Take" rate (as applicable)
  - Immunogenicity
  - Animal models (as needed)

Safety Database for Preventive Vaccines

- Target populations
  - Size
  - Usually healthy, often all ages
- Risk/benefit (e.g., risk of disease vs. risk of adverse event from vaccine)
- For licensure, typically have data on thousands, ideally from randomized, well-controlled studies
- Data quality important

Efficacy Data for New Smallpox Vaccines

- Epidemiology precludes “field trials”
- Cannot conduct human challenge/protection studies
- Need “bridging” studies or efficacy surrogates

Efficacy of Historical Smallpox Vaccines

- No well-controlled trials conducted with historical smallpox vaccines
- Protection correlated with presence of vaccination scar, which results from the classic Jennerian vesicle or so-called “vaccine take”
- Use of standardized vaccines (including those derived from NYCBH strain) led to eradication of smallpox

Clinical Evaluation for Licensure of New "2nd Generation" Smallpox Vaccines (U.S.)

- For vaccines derived from NYC Board of Health strain (e.g., Wyeth's Dryvax®) or other strains demonstrated to have efficacy:
  - Historical experience using Wyeth Dryvax® provides a "gold standard" for comparison
  - Efficacy based on comparative clinical studies of the new vaccine with Dryvax® ("take" rates, immunologic responses such as neutralizing antibody)
  - Safety data will have to be collected and evaluated to support licensure
  - Stringent animal models of efficacy not required for these types of vaccines

Clinical Evaluation for Licensure of New "3rd Generation" Smallpox Vaccines (U.S.)

- "2nd generation" vaccines may cause serious adverse reactions similar to historical vaccine
- Desire for safer vaccines that may be targeted toward populations for whom the "2nd generation" vaccines (derived from strains with proven efficacy) are contraindicated or present an increased risk of adverse reactions
- Evaluation of new vaccines derived from strains (e.g., Modified Vaccinia Ankara) with no previous demonstration of efficacy is more complex
- FDA has published a final rule that allows use of animal efficacy data in lieu of human efficacy data when scientifically appropriate

Final Rule: New Drug and Biological Products; Evidence needed to demonstrate effectiveness when human efficacy studies are not ethical or feasible ("Animal Efficacy Rule")

- For drugs and biologicals intended to reduce or prevent serious or life-threatening conditions caused by lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substance
- Human efficacy trials not feasible or ethical
- Efficacy based on adequate and well-controlled animal trials if results establish that product reasonably likely to provide clinical benefit to humans
- Safety and pharmacokinetic (e.g. immunogenicity) data in humans still necessary

Animal Efficacy Rule (cont.)

Animal studies can be used to support efficacy when

- **Well understood pathophysiological mechanism for toxicity and its prevention by product**
- **Effect demonstrated in more than one animal species is expected to react with response predictive for humans (single species acceptable in certain circumstances)**
- **Animal endpoint clearly related to desired benefit in humans**
- **Data on pharmacokinetics and -dynamics of product in animals and humans sufficiently well-understood to allow selection of effective dose in humans**

Clinical Evaluation for Licensure of New "3rd Generation" Smallpox Vaccines (cont.)

For smallpox vaccines derived from strains with no previous demonstration of efficacy

- **No well established non-human primate (NHP) model with variola (variola/monkey model requires high doses of variola, results in accelerated infection not similar to smallpox)**
- **A monkeypox challenge in NHP, a 2nd animal model, and supporting in vitro studies (e.g., neutralization of variola with human vaccinee sera) may provide basis for efficacy**
- **Human immune response data important**
- **Case has to be made that animal models using non-variola orthopox challenge are relevant to efficacy of vaccine in humans**
- **Human safety data needed**

Conclusions

- Historical smallpox vaccines (e.g., grown on calf skin) no longer manufactured in the U.S.
- To date, new smallpox vaccines intended for U.S. licensure are cell substrate based
- Efficacy of new vaccines derived from strains with demonstrated efficacy based on comparison of take rates and immune response with licensed vaccine (Dryvax®) in randomized, blinded studies
- Efficacy of new vaccines derived from strains without demonstrated efficacy can be based on animal efficacy data (if scientifically appropriate), in addition to comparative human immune responses
- As for any biologic, licensure of new smallpox vaccines requires demonstration of safety, efficacy, and quality and consistency of manufacturing